I. Amendments to the Specification:

Please replace the paragraph starting on page 1, line 5, with the following amended paragraph:

This application is a continuation of U.S. Patent Application Serial No. 09/781,081, filed on February 8, 2001, now U.S. Patent No. 6,696,088, which claims benefit of U.S. Provisional No. 60/181,369, filed February 8, 2000, the disclosure of which is hereby incorporated by reference in its entirety.

Please replace the paragraph starting on page 3, line 33, with the following amended paragraph:

There have previously been attempts in the art to control the abuse potential associated with opioid analgesics. For example, the combination of pentazocine and naloxone has been utilized in tablets available in the United States, commercially available as ~~Talwin® Nx~~ TALWIN® NX (pentazocine hydrochloride and naloxone) from Sanofi-Winthrop. ~~Talwin® Nx~~ TALWIN® NX (pentazocine hydrochloride and naloxone) contains pentazocine hydrochloride equivalent to 50 mg base and naloxone hydrochloride equivalent to 0.5 mg base. ~~Talwin® Nx~~ TALWIN® NX (pentazocine hydrochloride and naloxone hydrochloride) is indicated for the relief of moderate to severe pain. The amount of naloxone present in this combination has low activity when taken orally, and minimally interferes with the pharmacologic action of pentazocine. However, this amount of naloxone given parenterally has profound antagonistic action to narcotic analgesics. Thus, the inclusion of naloxone is intended to curb a form of misuse of oral pentazocine which occurs when the dosage form is solubilized and injected. Therefore, this dosage has lower potential for parenteral misuse than previous oral pentazocine formulations. However, it is still subject to patient misuse and abuse by the oral route, for example, by the patient taking multiple doses at once. A fixed combination therapy comprising tilidine (50 mg) and naloxone (4 mg) has been available in Germany for the management of severe pain since 1978 (~~Valoron®N~~ VALORON®N (tilidine and naloxone), Goedecke). The rationale for the combination of these drugs is effective pain relief and the prevention of tilidine addiction through naloxone-induced antagonisms at the morphine receptor. A fixed combination of buprenorphine and naloxone was

introduced in 1991 in New Zealand (~~Temgesic®Nx~~ TEMGESIC®NX (buprenorphine and naloxone), Reckitt & Colman) for the treatment of pain.

Please replace the paragraph starting on page 23, line 15, with the following amended paragraph:

A common dosage form of hydrocodone is in combination with acetaminophen, and is commercially available, e.g., as ~~Lortab®~~ LORTAB® (hydrocodone/acetaminophen tablets) in the U.S. from UCB Pharma, Inc. as 2.5/500 mg, 5/500 mg, 7.5/500 mg and 10/500 mg hydrocodone/acetaminophen tablets. Tablets are also available in the ratio of 7.5 mg hydrocodone bitartrate and 650 mg acetaminophen; and 7.5 mg hydrocodone bitartrate and 750 mg acetaminophen. Hydrocodone in combination with aspirin is given in an oral dosage form to adults generally in 1-2 tablets every 4-6 hours as needed to alleviate pain. The tablet form is 5 mg hydrocodone bitartrate and 224 mg aspirin with 32 mg caffeine; or 5 mg hydrocodone bitartrate and 500 mg aspirin. A relatively new formulation comprises hydrocodone bitartrate and ibuprofen. ~~Vicoprofen®~~ VICOPROFEN® (hydrocodone bitartrate and ibuprofen), commercially available in the U.S. from Knoll Laboratories, is a tablet containing 7.5 mg hydrocodone bitartrate and 200 mg ibuprofen. The present invention is contemplated to encompass all such formulations, with the inclusion of the opioid antagonist particles coated with a coating that renders the antagonist substantially non-releasable.

Please replace the paragraph starting on page 23, line 36, with the following amended paragraph:

Oxycodone is commercially available in the United States, e.g., as ~~Oxycontin®~~ OXYCONTIN® (oxycodone hydrochloride) from Purdue Pharma L.P. as controlled-release tablets for oral administration containing 10 mg, 20 mg, 40 mg or 80 mg oxycodone hydrochloride, and as ~~OxyIR®~~ OXYIR® (oxycodone hydrochloride), also from Purdue Pharma L.P., as immediate-release capsules containing 5 mg oxycodone hydrochloride. The present invention is contemplated to encompass all such formulations, with the inclusion of an opioid antagonist in a substantially non-releasable form.

Please replace the paragraph starting on page 25, line 18, with the following amended paragraph:

Naltrexone is commercially available in tablet form (~~Revia®~~ REVIA® (naltrexone hydrochloride tablets), DuPont) for the treatment of alcohol dependence and for the blockade of exogenously administered opioids. See, e.g., ~~Revia~~ REVIA® (naltrexone hydrochloride tablets). Physician's Desk Reference 51.sup.st ed., Montvale, N.J. "Medical Economics" 1997; 51:957-959. A dosage of 50 mg ~~Revia®~~ REVIA® (naltrexone hydrochloride tablets) blocks the pharmacological effects of 25 mg IV administered heroin for up to 24 hours.

Please replace the paragraph starting on page 29, line 36, with the following amended paragraph:

An acrylic polymer useful for preparation of the opioid antagonist in a substantially non-releasable form includes, but are not limited to, acrylic resins comprising copolymers synthesized from acrylic and methacrylic acid esters (e.g., the copolymer of acrylic acid lower alkyl ester and methacrylic acid lower alkyl ester) containing about 0.02 to 0.03 mole of a tri (lower alkyl) ammonium group per mole of the acrylic and methacrylic monomers used. An example of a suitable acrylic resin is a polymer manufactured by Rohm Parma GmbH and sold under the ~~Eudragit® RS~~ EUDRAGIT® RS (acrylic resin) trademark. ~~Eudragit RS30D~~ EUDRAGIT RS30D (acrylic resin) is preferred. ~~Eudragit® RS~~ EUDRAGIT® RS (acrylic resin) is a water insoluble copolymer of ethyl acrylate (EA), methyl methacrylate (MM) and trimethylammoniumethyl methacrylate chloride (TAM) in which the molar ratio of TAM to the remaining components (EA and MM) is 1:40. Acrylic resins such as ~~Eudragit® RS~~ EUDRAGIT® RS (acrylic resin) may be used in the form of an aqueous suspension.

Please replace the paragraph starting on page 35, line 14, with the following amended paragraph:

One commercially-available aqueous dispersion of ethylcellulose is ~~Aquacoat®~~ AQUACOAT® (ethylcellulose) (FMC Corp., Philadelphia, Pa., U.S.A.). ~~Aquacoat®~~ AQUACOAT® (ethylcellulose) is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under

vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the ~~Aquacoat®~~ AQUACOAT® (ethylcellulose) with a suitable plasticizer prior to use.

Please replace the paragraph starting on page 35, line 23, with the following amended paragraph:

Another aqueous dispersion of ethylcellulose is commercially available as ~~Surelease®~~ SURELEASE® (ethylcellulose) (Colorcon, Inc., West Point, Pa., U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

Please replace the paragraph starting on page 36, line 17, with the following amended paragraph:

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as ~~Eudragit®~~ EUDRAGIT® (acrylic resin) from Rohm Tech, Inc. There are several different types of ~~Eudragit®~~ EUDRAGIT® (acrylic resin). For example, ~~Eudragit® E~~ EUDRAGIT® E (acrylic resin) is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. ~~Eudragit® L~~ EUDRAGIT® L (acrylic resin) is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. ~~Eudragit® S~~ EUDRAGIT® S (acrylic resin) does not swell at about pH<6.5 and is soluble at about pH>7. ~~Eudragit® RL~~ EUDRAGIT® RL (acrylic resin) and ~~Eudragit® RS~~ EUDRAGIT® RS (acrylic resin) are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with ~~Eudragit® RL and RS~~ EUDRAGIT® RL AND RS (acrylic resin) are pH-independent.

Please replace the paragraph starting on page 36, line 29, with the following amended paragraph:

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames ~~Eudragit® RL30D~~ EUDRAGIT® RL30D (acrylic resin) and ~~Eudragit® RS30D~~ EUDRAGIT® RS30D (acrylic resin), respectively. ~~Eudragit® RL30D~~ EUDRAGIT® RL30D (acrylic resin) and ~~Eudragit® RS30D~~ EUDRAGIT® RS30D (acrylic resin) are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in ~~Eudragit® RL30D~~ EUDRAGIT® RL30D (acrylic resin) and 1:40 in ~~Eudragit® RS30D~~ EUDRAGIT® RS30D (acrylic resin). The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. ~~Eudragit® RL/RS~~ EUDRAGIT® RL/RS (acrylic resin) mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

Please replace the paragraph beginning on page 37, line 8, with the following amended paragraph:

The ~~Eudragit® RL/RS~~ EUDRAGIT® RL/RS (acrylic resin) dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% ~~Eudragit® RL~~ EUDRAGIT® RL (acrylic resin), 50% ~~Eudragit® RL~~ EUDRAGIT® RL (acrylic resin) and 50% ~~Eudragit® RS~~ EUDRAGIT® RS (acrylic resin), and 10% ~~Eudragit® RL~~ EUDRAGIT® RL (acrylic resin) :~~Eudragit®~~ 90% EUDRAGIT® RS (acrylic resin). Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, ~~Eudragit® L~~ EUDRAGIT® L (acrylic resin).

Please replace the paragraph beginning on page 38, line 5, with the following amended paragraph:

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate NF XVI, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as ~~Eudragit® RL/RS~~ EUDRAGIT® RL/RS (acrylic resin) lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

Please replace the paragraph beginning on page 38, line 35, with the following amended paragraph:

Spheroids or beads coated with an opioid agonist may be prepared, e.g., by dissolving the drug in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the opioid to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropylmethylcellulose, etc. with or without colorant (e.g., ~~Opadry®~~ OPADRY® (hydroxypropylmethylcellulose), commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

Please replace the paragraph beginning on page 39, line 16, with the following amended paragraph:

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as ~~Aquacoat®~~ AQUACOAT® (ethylcellulose) or ~~Surelease®~~ SURELEASE® (ethylcellulose), may be used. If ~~Surelease®~~ SURELEASE® (ethylcellulose) is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as ~~Eudragit®~~ EUDRAGIT® (acrylic resin) can be used.

Please replace the paragraph beginning on page 39, line 23 with the following amended paragraph:

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, color may be added to ~~Aquacoat®~~ AQUACOAT® (ethylcellulose) via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to water soluble polymer solution and then using low shear to the plasticized ~~Aquacoat®~~ AQUACOAT® (ethylcellulose). Alternatively, any suitable method of providing color to the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

Please replace the paragraph beginning on page 39, line 36, with the following amended paragraph:

Plasticized hydrophobic material may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined controlled release of said therapeutically active agent when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the therapeutically active agent, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as ~~Opadry®~~ OPADRY® (hydroxypropylcellulose), is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

Please replace the paragraph beginning on page 42, line 6, with the following amended paragraph:

Of these polymers, acrylic polymers, especially ~~Eudragit® RSPO~~ EUDRAGIT® RSPO (acrylic resin)-the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic material.

Please replace the paragraph beginning on page 45, line 12, with the following amended paragraph:

In yet other alternative embodiments, a spheronizing agent, together with the active ingredient can be spheronized to form spheroids. Microcrystalline cellulose is preferred. A suitable microcrystalline cellulose is, for example, the material sold as ~~Avicel PH 101~~ AVICEL PH 101 (microcrystalline cellulose) (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredient and spheronizing agent, the spheroids may also contain a binder.

Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropylcellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In such embodiments, the sustained release coating will generally include a hydrophobic material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

Please replace the paragraph beginning on page 52, line 17, with the following amended paragraph:

2. Blending Mix Naltrexone HCl, ~~Eudragit~~ EUDRAGIT (acrylic resin), and milled Stearyl Alcohol in a twin shell blender.

Please replace the paragraph beginning on page 56, line 14, with the following amended paragraph:

1. Solution Preparation Plasticize the ~~Eudragit~~ EUDRAGIT (acrylic resin) with Triacetin by mixing.

Please replace the paragraph beginning on page 57, line 17, with the following amended paragraph:

2. Blending Mix Hydromorphone HCl, ~~Eudragit~~ EUDRAGIT (acrylic resin), Ethycellulose and milled Stearyl Alcohol in a twin shell blender.

Please replace the paragraph beginning on page 60, line 14, with the following amended paragraph:

1. Solution Preparation Plasticize the ~~Eudragit~~ EUDRAGIT (acrylic resin) with Triacetin by mixing.

Please replace the paragraph beginning on page 61, line 14, with the following amended paragraph:

1. Solution Preparation Plasticize the ~~Eudragit~~ EUDRAGIT (acrylic resin) with Triacetin by mixing.

Please replace the paragraph beginning on page 62, line 17, with the following amended paragraph:

2. Blending Mix Hydromorphone HCl, ~~Eudragit~~ EUDRAGIT (acrylic resin), Ethycellulose and milled Stearyl Alcohol in a twin shell blender.

Please replace the paragraph beginning on page 63, line 6, with the following amended paragraph:

Controlled Release Oxycodone Hydrochloride 10 mg Tablets--Organic Manufacture Oxycodone hydrochloride (10 mg/tablet) and spray dried lactose (71.25 mg/tablet) are transferred into an appropriate sized mixer and mix for approximately 6 minutes. ~~Eudragit®~~ EUDRAGIT® RS PM (acrylic resin) powder (6 mg/tablet) is dispersed in ethanol. While the powders are mixing, the powders are granulated with the dispersion and the mixing continued until a moist granular mass is formed. Additional ethanol is added if needed to reach granulation end point. The granulation is transferred to a fluid bed dryer and dried at 30 C, and then passed through a 12-mesh screen. The remaining ~~Eudragit®~~ EUDRAGIT® RS PM (acrylic resin) (9 mg/tablet) is dispersed in a solvent of 90 parts ethanol and 10 parts purified water; and sprayed onto the granules in the fluid bed granulator/dryer at 30 C. Next, the granulate is passed through a 12-mesh screen. Stearyl alcohol (25 mg/tablet) is melted at approximately 60-70 C. The warm granules are returned to the mixer. While mixing, the melted stearyl alcohol is added. The coated granules are removed from the mixer and allowed to cool. Thereafter, they are passed through a 12-mesh screen. Next, the granulate is mixed with naloxone particles (approximately 1-5 mg per tablet) coated with a coating that renders naloxone substantially non-releasable, and pharmaceutically desirable

tabletting excipients, e.g., talc and magnesium stearate in a suitable blender and compressed into tablets.

Please replace the paragraph beginning on page 63, line 33, with the following amended paragraph:

Preferably, the coating composition comprises ~~Eudragit®~~ EUDRAGIT® RS (acrylic resin), which may be used in the form of an aqueous suspension and in combination with a plasticizer such as, e.g., acetyl triethylcitrate and/or acetyl tributyl citrate.

Please replace the paragraph beginning on page 64, line 5, with the following amended paragraph:

Preferably, the coating composition comprises ~~Eudragit®~~ EUDRAGIT® RS (acrylic resin), which may be used in the form of an aqueous suspension and in combination with a plasticizer such as, e.g., acetyl triethylcitrate and/or acetyl tributyl citrate.

Please replace the paragraph beginning on page 70, line 16, with the following amended paragraph:

1. Disperse povidone and ~~Eudragit~~ EUDRAGIT RS30D (acrylic resin) in water. Blend morphine sulfate and lactose.

Please replace the paragraph beginning on page 70, line 20, with the following amended paragraph:

4. Disperse ~~Eudragit~~ EUDRAGIT RS30D (acrylic resin), RL 30D, Triethyl citrate, talc and triethyl citrate in water. Coat the above beads in a fluid bed coated with Wurster insert.

Please replace the paragraph beginning on page 71, line 16, with the following amended paragraph:

2. Blending Mix Naltrexone HCl, ~~Eudragit~~ EUDRAGIT (acrylic resin), milled Stearyl Alcohol, Stearic Acid and BHT in a twin shell blender.

Please replace the paragraph beginning on page 74, line 16, with the following amended paragraph:

2. Blending Mix Hydromorphone HCl, ~~Eudragit~~ EUDRAGIT (acrylic resin), Ethycellulose and milled Stearyl Alcohol in a twin shell blender.

Please replace the paragraph beginning on page 76, line 9, with the following amended paragraph:

2. Disperse ~~Eudragit L~~ EUDRAGIT L (acrylic resin), Tributyl citrate, and talc in water. Spray the dispersion onto the drug-loaded beads in the fluid bed coater.

Please replace the paragraph beginning on page 76, line 11, with the following amended paragraph:

3. Disperse ~~Eudragit~~ EUDRAGIT RS (acrylic resin), tributyl citrate, and talc in water. Spray the dispersion onto the beads in the fluid bed coater.